

In the final Office Action, the Examiner has maintained two rejections of the claims under 35 U.S.C. § 103. In response, Applicants respectfully submit the following remarks.

***The Rejection Under 35 U.S.C. § 103 Must Be Withdrawn***

The Examiner has rejected the claims under 35 U.S.C. § 103, as being obvious over Wallach *et al.* (reference AN1) for the reasons made of record in papers number 4 and 8. The Examiner previously stated that Wallach taught the purification of TNF binding protein from urine and a partial amino acid sequence of the purified protein. The Examiner has contended that the cloning of the DNA encoding the protein of Wallach was within the skill in the art at the time of the present invention and, therefore, such a DNA molecule is obvious. The Examiner believes that one of ordinary skill in the art could have isolated the DNA encoding the TNF binding protein using the partial amino acid sequence and the methods outlined in Wallach. Alternatively, the Examiner has contended that the entire amino acid sequence of the isolated protein of Wallach could have been determined using known methodologies and, from this sequence, the DNA sequence encoding same could have been determined.

Applicants respectfully traverse this rejection based on the following remarks.

The present invention is directed to DNA molecules which encode a soluble form of the TNF receptor. This soluble form of the TNF receptor, encoded by the

DNA molecules of the present invention, maintains the ability to bind TNF. The nucleotide sequences of the presently claimed DNA molecules are not taught by the references cited by the Examiner. Applicants respectfully submit that there is sufficient evidence within the present record which demonstrates that extraordinary skill was required to obtain the DNA molecules of the present invention. The extraordinary skill that was required to reduce to practice the claimed nucleic acid molecules renders the claimed invention non-obvious.

Applicants previously made of record a second application of Wallach (reference AO1, hereinafter Wallach 2) to demonstrate that the isolation of DNA encoding a soluble form of the TNF binding protein was not obvious to one of ordinary skill in the art because more than two years had elapsed between the two Wallach applications. Applicants further pointed to Wallach 2 as demonstrating that the practicing of the methods suggested by the Examiner would not have yielded the presently claimed sequences because the soluble TNF binding protein of Wallach is the product of proteolytic cleavage of a membrane bound protein and is not encoded by a discrete mRNA molecule. Lastly, Applicants submit that Wallach 2 demonstrates the extraordinary skill which was required to obtain the DNA molecules of the present invention.

To obtain the DNA molecules of the present invention as suggested by the Examiner, a skilled artisan must be able to use the N-terminal amino acid sequence of Wallach 1 to obtain DNA sequence information. At page 7, line 23, of Wallach 2, it is disclosed that three specifically designed, degenerate, overlapping probes, corresponding to nucleotide sequences encoding the N-terminal amino

acids, were used to screen several cDNA libraries. One of the libraries screened, derived from randomly primed, human colon mRNA, yielded four phages with overlapping inserts of similar size.

To be successful in isolating the four partial clones, Wallach 2 had to screen "several libraries." Nowhere within any of the cited references (Wallach, as well as the references raised in the second prior art rejection) is there any teaching which would have directed a skilled artisan to choose a cDNA library generated from human colon mRNA for screening. Conversely, since the soluble TNF binding protein of Wallach 1 was isolated from urine, cells of the colenary tract would not have been expected to be a source of expression for this protein. A lack of success would have resulted from the improper choice of source mRNA for the libraries screened because Wallach 2 discloses that human colon mRNA was the only one of several originally screened libraries which yielded partial fragments of the desired sequence. As such, a skilled artisan would have needed this "extraordinary information" to be successful in employing the procedures as proposed by the Examiner.

In addition to library choice, Wallach 2 disclosed that three overlapping probes had to be designed and used (see figure 1A of Wallach 2). The choice of probe sequence, probe length, probe degeneracy, probe number, and degree of overlap which was required to yield only four partial, overlapping fragments of the entire sequence clearly establishes the non-routine nature of isolating the present DNA molecules. Although the identification of nucleotide sequence information is sometimes straight forward, generally the isolation of a particular sequence is

considered unpredictable within the art. This sentiment was reflected in the Federal Circuit decision of *Amgen v. Chugai*, 18 USPQ2d 1016 (1991) where the court found that conception and reduction to practice are contemporaneous with identifying the nucleic acid sequences encoding the functional proteins, due to the uncertainty of obtaining such nucleic acid molecules.

At page 7, lines 29-36, Wallach 2 continues discussing the isolation of nucleic acid molecules by disclosing that further screening of the colon cDNA library was performed using longer probes based on the additional sequence information obtained from the partial fragments isolated above. However, "none of them [additionally isolated clones] provided further sequence information," line 35. To solve the lack of success in obtaining complete sequence information, Wallach 2 chose another element which is not taught by the cited references, namely to screen a library derived from oligo dT and randomly primed CEM lymphocyte mRNA. As with the only other successfully screened cDNA library, there is nothing in the cited references which would suggest to a skilled artisan to choose this mRNA source for the library which is screened. Nothing within the art suggested that the source of expression of the urine protein of Wallach 1 would be a clonal lymphocytic cell line.

Wallach isolated five cDNA inserts from the CEM lymphocyte library, the longest of which was sequenced and found to encode the TNF receptor, an integral membrane protein. Applicants' claims do not read on sequences which encode the membrane bound TNF receptor isolated by Wallach. Applicants claim DNA molecules with specified nucleotide sequences which encode a soluble form of the

TNF receptor. Wallach 2 clearly demonstrates that the use of the N-terminal sequence to design a probe would not have yielded the presently claimed molecules.

In order to obtain one of the sequences within the present claims, Wallach 2 had to subclone "the gene from position 256 to position 858" (page 9, line 1 of Wallach 2) from the isolated and sequenced cDNA (position 256 to 858 corresponds to the sequence in claim 6 of the present application). The need to subclone from a larger cDNA is not taught by any of the references cited by the Examiner. Conversely, Wallach chose to characterize the largest insert because the art taught that the larger the insert, the more complete the sequence information.

Alternatively, at page 2 of paper number 8, the Examiner has contended that the nucleotide sequence of DNA molecules which encode a soluble TNF receptor could have been obtained by first determining the amino acid sequence of the isolated protein of Wallach and then determining the encoding DNA sequence using a codon table. Applicants respectfully submit that Wallach 2 demonstrates that barriers existed which prevented a reasonable expectation of success with the method suggested by the Examiner.

At page 12, Table 1 of Wallach 2, partial amino acid sequence information is provided which was obtained from the purified TNF binding protein (Wallach proceeded as suggested by the Examiner). Despite the use of purified protein, Wallach 2 was not able to determine the entire amino acid sequence of all 157 amino acid residues of the soluble TNF binding protein. Further, because of the

fragmentary nature of the sequence information obtained, Wallach was unable to align the partial sequences. As such, a skilled artisan could not have used the information of Table 1 to obtain the DNA molecules of the present invention. The inability of Wallach 2 to obtain a complete, aligned amino acid sequence for the TNF binding protein demonstrates the pitfalls associated with the methods suggested by the Examiner.

In summary, numerous barriers would have prevented a skilled artisan from having a reasonable expectation of success in obtaining the presently claimed DNA molecules using the disclosure of Wallach and general recombinant DNA methods. The second application of Wallach illustrates the numerous obstacles not taught or suggested in the cited references, the solutions of which were required to reduce to practice a DNA molecule of the present invention. Further, the authors of the cited reference were unable to obtain the entire amino acid sequence of the TNF binding protein using known methods. As such, the authors chose not to further sequence the purified protein as a means of obtaining nucleotide sequence information. Thus, the rejection is in error and must be withdrawn.

The Examiner has further rejected the claims under 35 U.S.C. § 103 as being unpatentable over Olsson, in view of Wallach or any other molecular biology laboratory techniques book or manual for essentially the same reasons as expounded for the above rejection.

Applicants respectfully traverse this rejection based on the following remarks.

The soluble TNF binding proteins of Wallach and Olsson are the same proteins. Further, Olsson contains the same deficiencies as Wallach with regard to the elements required to reduce to practice the presently claimed DNA molecules.

As argued above and demonstrated by Wallach 2, even if a skilled artisan was successful in cloning a DNA molecule which encodes the TNF binding protein, the artisan would have obtained DNA molecules encoding the *membrane-bound TNF receptor*. The soluble TNF binding protein appears to be derived from the shedding of the TNF receptor which occurs *in vivo* via proteolytic cleavage. The shed TNF receptor is the protein described by Wallach 1 and Olsson. As such, a cDNA library will not contain discrete sequences encoding the soluble TNF binding protein.

Applicants had to modify the sequences encoding the membrane bound receptor to obtain a DNA molecule which encodes a soluble TNF binding protein. Olsson, Wallach, as well as the secondary references do not teach or suggest that such modifications would be required.

Applicants respectfully submit that the two rejections under 35 U.S.C. § 103 satisfy the "obvious to try" standard, a standard insufficient to render obvious a claimed invention. According to the Federal Circuit, "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). An invention is obvious to try and not obvious where the prior art gives no indication of which parameters

are critical or no direction as to which of the many possible choices is likely to be successful.

In holding that the present composition claims are obvious over generic teachings of methods for reducing to practice DNA molecules, the Examiner is ignoring the last sentence of the first paragraph of 35 U.S.C. § 103 where it is clearly stated that "patentability shall not be negated by the manner in which the invention was made." The Court of Appeals for the Federal Circuit has recently reversed a similar rejection where a DNA molecule stood rejected over an entire amino acid sequence and generic recombinant methods holding that "the PTO's focus on Bell's method is misplaced. Bell claims compositions, and the issue of obviousness of the claimed compositions, not the method by which they are made." *In re Bell*, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993). The court in *Bell* relied upon *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985) for the proposition that "the patentability of a product does not depend on the method of production." In a similar fashion, the Examiner should not be focusing and rejecting the present composition claims in light of generic methods in the art, particularly in light of the teaching of Wallach 2.

Applicants have reduced to practice previously unknown DNA molecules which encode a protein normally produced as a proteolytic by-product. The proteolytic by-product is not encoded by discrete, naturally occurring nucleic acid molecules. As such, procedures which are directed to obtaining a naturally occurring nucleotide molecule would fail in reducing to practice the presently claimed DNA molecule.

In the present case, the critical features of library source selection, probe design, and the fact that the TNF binding protein from urine is a proteolytic cleavage product and not encoded by a discrete mRNA, are not taught or suggested by the cited references. Thus, a finding of obviousness is not supported by the cited references.

### ***Conclusion***

Applicants respectfully submit that all the bases for rejection have been overcome by the above remarks. Reconsideration of the application is respectfully requested, and passage of the application to issuance is earnestly solicited.

Respectfully submitted,

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